Thyroid function testing and management during and after pregnancy among women without thyroid disease before pregnancy

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ABSTRACT

BACKGROUND: Screening in pregnancy for subclinical hypothyroidism, often defined as thyroid-stimulating hormone (TSH) greater than 2.5 mIU/L or greater than 4.0 mIU/L, is controversial. We determined the frequency and distribution of TSH testing by gestational age, as well as TSH values associated with treatment during pregnancy and the frequency of postpartum continuation of thyroid hormone therapy.

METHODS: We performed a retrospective cohort study of pregnancies in Alberta, Canada. We included women without thyroid disease who delivered between October 2014 and September 2017. We used delivery records, physician billings, and pharmacy and laboratory administrative data. Our key outcomes were characteristics of TSH testing and the initiation and continuation of thyroid hormone therapy. We calculated the proportion of pregnancies with thyroid testing and the frequency of each specific thyroid test.

RESULTS: Of the 188 490 pregnancies included, 111 522 (59.2%) had at least 1 TSH measurement. The most common time for testing was at gestational week 5 to 6. Thyroid hormone therapy was initiated at a median gestational age of 7 (interquartile range 5–12) weeks. Among women with first TSH measurements of 4.01 to 9.99 mIU/L who were not immediately treated, the repeat TSH measurement was 4.00 mIU/L or below in 67.9% of pregnancies. Thyroid hormone was continued post partum for 44.6% of the women who started therapy during their pregnancy.

INTERPRETATION: The findings of our study suggest that current practice patterns may contribute to overdiagnosis of hypothyroidism and overtreatment during pregnancy and post partum.

In the past 3 decades, undiagnosed or subclinical hypothyroidism during pregnancy has been variably associated with adverse maternal and childhood outcomes in observational studies.[1,2] However, in the absence of strong evidence showing a benefit of levothyroxine therapy for subclinical hypothyroidism in pregnancy, confusion has arisen about the utility of screening using thyroid-stimulating hormone (TSH) during pregnancy. A common challenge with TSH screening is that it identifies many women with minor elevation of TSH, specifically subclinical hypothyroidism. Subclinical hypothyroidism in pregnancy has a variety of definitions, such as TSH greater than 2.5 mIU/L, TSH greater than 4.0 mIU/L or TSH above the upper limit of the assay-specific reference range for gestational age in combination with a normal level of free thyroxine.[3] Recent evidence from large, high-quality randomized controlled trials (RCTs) has consistently shown no benefit for the mother or child from levothyroxine treatment of pregnant women with subclinical hypothyroidism, hypothyroxinemia or presence of thyroid peroxidase antibodies.[4–9]

Known changes in thyroid physiology during pregnancy have led to controversy about the upper TSH reference limit in pregnancy. Specifically, human chorionic gonadotropin is a weak TSH receptor stimulator that contributes to a decline in TSH after 7 weeks' gestation and a return of TSH to pre-pregnancy ranges after human chorionic gonadotropin peaks, at about 10 to 11 weeks' gestation. Studies to establish pregnancy-specific reference ranges, which were initially done in the United States and Europe late in the first trimester or early in the second trimester, led to the recommendation to use a TSH upper limit of 2.5 mIU/L in the first trimester and 3.0 mIU/L in the second and third trimesters.[10–12] Subsequent studies in other populations and earlier in pregnancy found that these upper limits were not appropriate for all ethnicities and that their use, especially early in the first trimester, could lead to misclassification of up to 37% of pregnant women as having subclinical hypothyroidism.[13]

Controversy about both the benefit of levothyroxine treatment and the upper limit of TSH during pregnancy, as well as the results of newer, high-quality RCTs, has contributed to discordance among professional societies' guidelines regarding universal screening, as well as confusion about the TSH thresholds and thyroid peroxidase antibody status that should trigger treatment.[3,14] All of these factors may contribute to substantial variation in clinical practice. Importantly, thyroid hormone therapy started during pregnancy is often continued post partum, although the extent of this practice is unknown.

There is a paucity of data about the routine clinical practice of thyroid testing and patterns for initiation of thyroid hormone therapy during pregnancy and its continuation post partum. Therefore, we aimed to describe the current management of thyroid testing and treatment during pregnancy in women without thyroid disease before pregnancy. Specifically, we aimed to determine the frequency and distribution of TSH testing by gestational age, the TSH measurement values associated with initiation of thyroid hormone therapy and the frequency of postpartum continuation of thyroid hormone therapy after initiation during pregnancy.

Methods

Study design, setting and population

In this retrospective cohort study, we collected administrative data for women aged 15 to 49 years who delivered in Alberta, Canada, between Oct. 1, 2014, and Sept. 30, 2017. Alberta has an ethnically diverse population of more than 4 million people.[15]

Potential participants were excluded if they had evidence of thyroid disease in the 2 years before conception, defined as any of the following: filled a prescription for any thyroid medication (levothyroxine, desiccated thyroid, liothyronine, methimazole or propylthiouracil); had any *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) codes for thyroid disease (E00–E07, e35.0, e89.0, r94.6, t38.1, t38.1, t38.2, y42.2, y42.3) or the equivalent *International Classification of Diseases, 9th Revision* (ICD-9) codes for outpatient billing data (i.e., 240–249); or had a TSH measurement less than 0.20 or greater than 5.00 mIU/L (chosen because these levels are outside the nonpregnant reference range).

Data sources

We used the Alberta Perinatal Health Program database to identify deliveries in Alberta. This database includes information from the provincial delivery records collected for all hospital births and home births attended by registered midwives in Alberta from 20 weeks' gestation. The Alberta Perinatal Health Program database is validated frequently, a process that includes validation with health records, vital statistics and registered midwives.[16] Using maternal personal health care numbers, we linked the data to the Discharge Abstract Database for hospitalization data; the province-wide laboratory databases from Alberta Health, Alberta Health Services and Alberta Precision Laboratories; the Pharmaceutical Information Network database for details on prescription medications; and physician claims for outpatient physician visits from Alberta Health.

Key definitions and outcome measures

The reference range for TSH in pregnancy was defined as 0.10 to 4.00 mIU/L. This definition was in keeping with the American Thyroid Association's 2017 guideline recommendations,[3] given that not all regions in the province have locally established, trimester-specific reference ranges and because of variations in the TSH assay used across the province. We defined the subclinical hypothyroid range of TSH as 4.01 to 9.99 mIU/L and overt hypothyroidism as TSH of 10.00 mIU/L or higher. We also analyzed TSH measurements in the range of 2.51 to 4.00 mIU/L, in keeping with the 2011 pregnancy guidelines of the American Thyroid Association.[11] We defined initiation of thyroid hormone therapy during pregnancy as the filling of a prescription for levothyroxine, desiccated thyroid or liothyronine after conception and before delivery. We defined continuation of thyroid hormone therapy post partum as the filling of a prescription for any of these medications after delivery within the first year post partum for pregnancies in which thyroid hormone therapy was initiated during the pregnancy.

Statistical analysis

We calculated the proportion of pregnancies with thyroid testing and the frequency of each specific thyroid test (e.g., TSH, thyroid peroxidase antibodies). We used univariable and multivariable logistic regression to examine the association between patient characteristics and TSH testing, and we used Mann–Whitney *U* testing to compare TSH results that were and were not associated with thyroid hormone initiation and repeat TSH testing in pregnancy. We performed all analyses using SPSS (IBM SPSS Statistics, IBM Corporation, version 25). A p value of less than 0.05 was considered statistically significant. We also performed a sensitivity analysis to examine the continuation of thyroid hormone therapy post partum, comparing 1 versus 2 or more prescriptions filled in the first postpartum year.

Ethics approval

Ethics approval was obtained from the Conjoint Health Research Ethics Board, University of Calgary (REB18–0223).

Results

A total of 188 490 deliveries were included in this cohort study (Figure 1). Of these, 111 522 (59.2%) had TSH measured at least once during the pregnancy, 10 685 (5.7%) had free thyroxine measured at least once during the pregnancy, and 4662 (2.5%) had thyroid peroxidase antibodies measured at least once during the pregnancy.

TSH testing

Maternal characteristics for deliveries with and without TSH testing during pregnancy are summarized in Table 1. Multiple logistic regression showed that women who were 35 years of age or older, who were nulliparous, who were from an urban area, who had gestational hypertension or who had other medical disorders were more likely to have TSH measured during pregnancy, whereas those who smoked were less likely to have TSH measured during pregnancy (Appendix 1, Table A1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.191664/-/DC1).

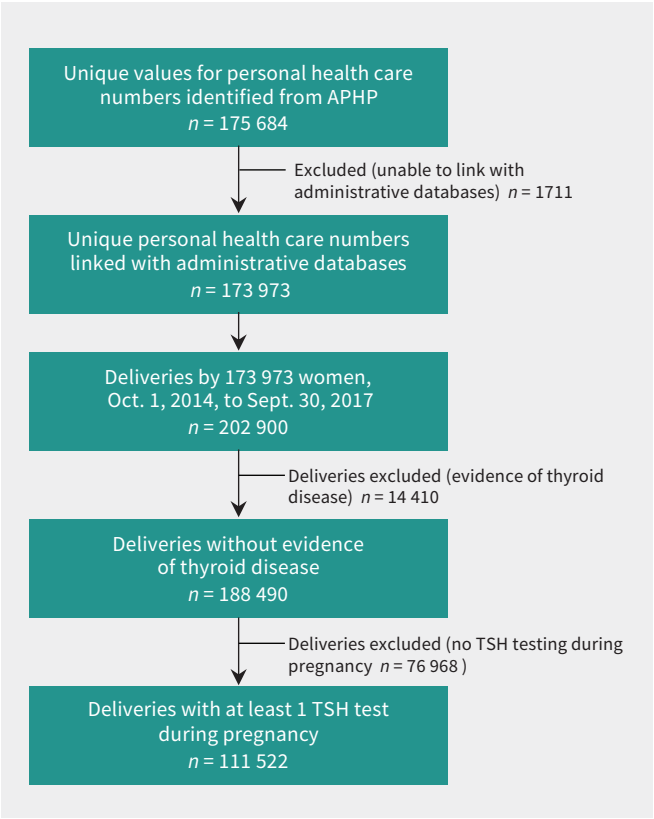

Figure 1: Flow diagram for derivation of the study population. Note: APHP = Alberta Perinatal Health Program, TSH = thyroid-stimulating hormone.

Among deliveries with at least 1 TSH test during pregnancy, the median number of TSH tests performed was 1 (interquartile range [IQR] 1–2). The most common time for testing was around gestational week 5 to 6 (Figure 2). The distribution of gestational age for TSH testing was bimodal for both the first and second TSH measurements (Figure 2 and Appendix 1, Figure A1, respectively).

The first TSH measurement was in the "normal pregnancy range," between 0.10 and 4.00 mIU/L, for 103 616 (92.9%) of deliveries that had TSH testing during the pregnancy. A total of 4417 (4.0%) had a first TSH measurement in the "subclinical hypothyroid range," between 4.01 and 9.99 mIU/L, and 1709 (1.5%) had a first TSH measurement in the "overt hypothyroid pregnancy range," 10.00 mIU/L or above (Table 2). The highest TSH measurement for each pregnancy is summarized in Table 2.

Initiation of thyroid hormone therapy

For a total of 5050 (4.5%) pregnancies with TSH testing, the women were started on thyroid hormone therapy. Those initiated on thyroid hormone therapy had a median of 4 (IQR 2–5) TSH measurements during pregnancy. Thyroid hormone therapy was initiated at a median gestational age of 7 (IQR 5–12) weeks. Women who initiated thyroid hormone therapy during pregnancy had their first TSH test earlier in gestation than women who had a TSH test but did not initiate thyroid hormone therapy (median 7 [IQR 5–12] v. 9 [IQR 6–13] wk; $p < 0.001$). Levothyroxine was the type of thyroid hormone therapy initiated in 5028 (99.6%) of these pregnancies. The mean dose of levothyroxine

Table 1: Maternal characteristics associated with deliveries with and without TSH testing during the pregnancy

Maternal characteristic	Group; no. (%) of deliveries* TSH tested *n* = 111 522	TSH not tested *n* = 76 968	OR (95% CI)
Age, yr, mean ± SD	30.2 ± 5.1	29.4 ± 5.4	NA
Age ≥ 35 yr	21 421 (19.2)	12 843 (16.7)	1.18 (1.16–1.21)
Urban residence†	79 934 (71.7)	44 495 (57.8)	1.85 (1.81–1.88)
Nulliparous	48 069 (43.1)	28 182 (36.6)	
Pre-pregnancy weight, kg‡			
≤ 45	1031 (0.9)	608 (0.8)	1.16 (1.05–1.28)
46–90	100 064 (90.2)	68 486 (89.7)	1.0 (Ref.)
≥ 91	9814 (8.8)	7215 (9.4)	0.93 (0.90–0.96)
Smoking	10 621 (9.5)	9971 (13.0)	0.69 (0.67–0.71)
Heart disease	591 (0.5)	332 (0.4)	1.20 (1.05–1.37)
Pre-pregnancy hypertension	1279 (1.1)	785 (1.0)	1.12 (1.03–1.23)
Gestational hypertension	6386 (5.7)	3669 (4.8)	1.21 (1.16–1.26)
Chronic kidney disease	116 (0.1)	63 (0.1)	1.24 (0.91–1.68)
Other medical disorders	9144 (8.2)	5015 (6.5)	1.28 (1.23–1.32)

Note: CI = confidence interval, NA = not applicable; OR = odds ratio, Ref. = reference category, SD = standard deviation, TSH = thyroid-stimulating hormone.
*Except where indicated otherwise. For all characteristics, data were missing for less than 1% of deliveries.
†Defined as > 50 000 residents.
‡Denominators used for calculating percentages for this variable were 110 909 and 76 309, respectively.

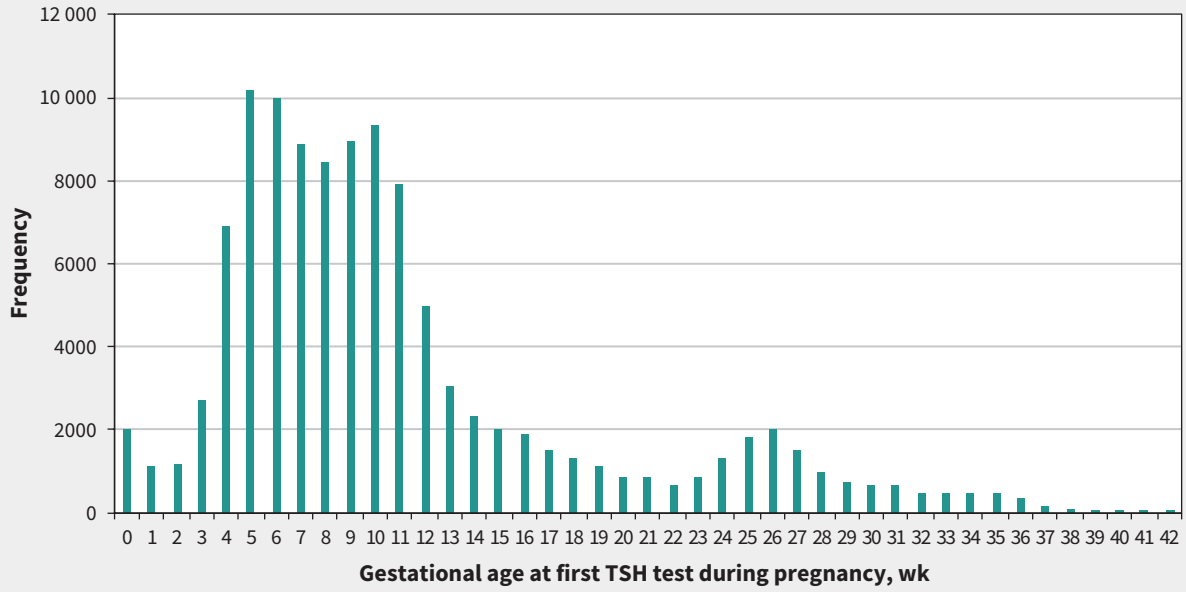

Figure 2: Gestational age at the time of first measurement of thyroid-stimulating hormone (TSH) in pregnancy.

Table 2: Initiation of thyroid hormone therapy during pregnancy and continued after delivery in relation to first and highest TSH values

	First or highest TSH value (mIU/L); no. (%) of deliveries*					
Variable	**< 0.10**	**0.10–2.50**	**2.51–4.00**	**4.01 –9.99**	**≥ 10.00**	**All**
By first TSH value during pregnancy	*n* = 1780	*n* = 88 534	*n* = 15 082	*n* = 4417	*n* = 1709	*n* = 111 522
Initiated on thyroid hormone	29 (1.6)	750 (0.8)	1520 (10.1)	2451 (55.5)	300 (17.6)	5050 (4.5)
Continued on thyroid hormone after delivery	10 (34.5)	357 (47.6)	499 (32.8)	1175 (47.9)	211 (70.1)	2252 (44.6)
Continued on thyroid hormone after delivery with ≥ 2 prescriptions in first year†	8 (27.6)	256 (34.1)	314 (20.7)	844 (34.4)	169 (56.3)	1591 (31.5)
By highest TSH value during pregnancy	*n* = 591	*n* = 87 835	*n* = 16 141	*n* = 4953	*n* = 2002	*n* = 111 522
Initiated on thyroid hormone	*n* < 5	532 (0.6)	1371 (8.5)	2783 (56.2)	362 (18.1)	5050 (4.5)
Continued on thyroid hormone after delivery	0 (0)	265 (49.8)	426 (31.1)	1312 (47.1)	249 (68.8)	2252 (44.6)
Continued on thyroid hormone after delivery with ≥ 2 prescriptions in first year†	0 (0)	191 (35.9)	270 (19.7)	932 (33.5)	198 (54.7)	1591 (31.5)

Note: TSH = thyroid-stimulating hormone.
*The denominator for calculating each percentage is the *n* value in the previous row (same column), unless otherwise indicated.
†The denominator for calculating each percentage in this row is the count of pregnancies with initiation of thyroid hormone therapy during the pregnancy (same column).

initiated in pregnancy was 44.1 (standard deviation 24.0) µg/day, and the median dose was 50 (IQR 25–50) µg/day. For the remaining 22 (0.4%) pregnancies, desiccated thyroid was prescribed.

Among the 16 141 pregnancies with a highest TSH value ranging from 2.51 to 4.00 mIU/L, thyroid hormone therapy was initiated during 1371 (8.5%) of the pregnancies (Table 2). Among the 1709 pregnancies with a first measured TSH value of 10.00 mIU/L or higher, thyroid hormone therapy was initiated during only 300 (17.6%) of the pregnancies (Table 2).

Pregnancies with first TSH in subclinical hypothyroid range

The management of pregnancies with initial TSH between 4.01 and 9.99 mIU/L (subclinical hypothyroid range) is displayed in Table 2 and Figure 3. Of the 4417 women with subclinical hypothyroid values, 2451 (55.5%) were initiated on thyroid hormone therapy. Measured patient characteristics, including TSH ordered by a family physician, parity, age, hypertension, weight and smoking, did not differ between patients who were and were not treated for a single minor elevated TSH value (Appendix 1, Table A2). Among

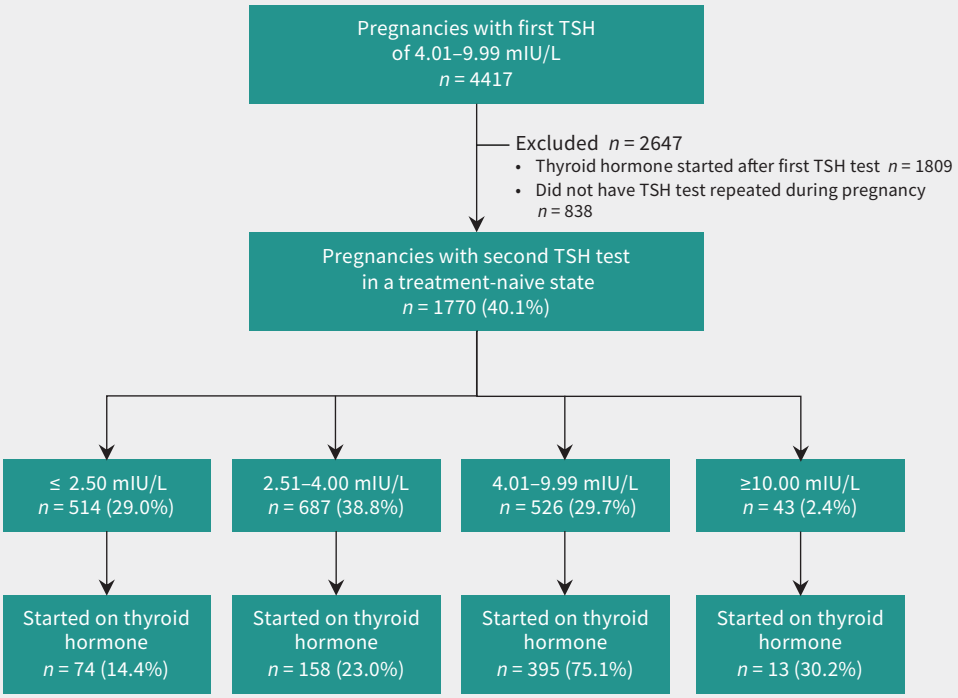

Figure 3: Follow-up testing of pregnant women with initial value for thyroid-stimulating hormone (TSH) between 4.01 and 9.99 mIU/L. Data are presented as number (%) of participants, with the denominator used to calculate each percentage being the *n* value in the preceding row.

women whose initial TSH was in the subclinical hypothyroid range, 1770 (40.1%) had repeat TSH testing in a treatment-naive state. These repeat measurements were performed at a median of 5 (IQR 3–9) weeks after the first TSH measurement. The repeat testing showed normalization, to 4.00 mIU/L or below, in 1201 (67.9%) cases (Figure 3). There was considerable overlap in the median TSH values that were and were not associated with repeat TSH testing in pregnancy (4.9 [IQR 4.3–5.8] v. 4.7 [IQR 4.3–5.4] mIU/L; Mann–Whitney *U* test, Z = –4.71, $p < 0.001$).

Thyroid peroxidase antibody measurements

Thyroid peroxidase antibodies were measured in 4662 (2.5%) of all pregnancies. When the result was positive, it was associated with initiation of thyroid hormone ($p < 0.001$). Details of this testing are summarized in Appendix 1, Table A3 and Table A4.

Continuation of thyroid hormone therapy post partum

Thyroid hormone therapy was continued during the first year post partum for 2252 (44.6%) of the 5050 deliveries with initiation of such therapy during the pregnancy (Table 2). Among the 1903 deliveries with initiation of thyroid hormone therapy during the pregnancy and highest TSH between 0.10 and 4.00 mIU/L, the therapy was continued post partum for 691 (36.3%). For levothyroxine started in pregnancy and continued post partum, the median dosage was 50 µg/day. For levothyroxine started in pregnancy and stopped post partum, the median dosage prescribed in pregnancy was 25 µg/day. In the postpartum period, TSH was 10.00 mIU/L or higher for only 5 women who started thyroid hormone therapy in pregnancy and continued post partum. A sensitivity analysis with filling of 2 or more prescriptions for thyroid hormone in the first year post partum also showed that treatment was commonly continued post partum (Table 2).

Interpretation

We found that among women who did not have thyroid disease before pregnancy, TSH testing was performed in more than half of all pregnancies, usually early in the first trimester. Thyroid hormone therapy for subclinical hypothyroidism (TSH 4.01–9.99 mIU/L) was most often initiated after only 1 TSH measurement, although TSH in this range frequently normalized without therapy. In addition, thyroid hormone therapy was frequently continued post partum. The practice of TSH testing early in the first trimester may be resulting in overdiagnosis and unnecessary thyroid hormone therapy during and after pregnancy.

Our population-based cohort study augments the study by Maraka and colleagues[17] of 7990 pregnant women with TSH measurements of 2.5 to 10 mIU/L. They found that 15.2% of the women received levothyroxine treatment during pregnancy, whereas we found that about 20% of women with TSH of 2.5 to 10 mIU/L were started on thyroid hormone therapy. Maraka and colleagues did not report on continuation of levothyroxine post partum.

The commonest timing of the first TSH measurement (5–6 wk gestation) and the median timing of thyroid hormone initiation (7 wk gestation) both occurred in a period when it is well established that TSH level falls rapidly because of normal physiologic changes of pregnancy.[3,13] This raises concerns about overmedicalization during pregnancy, given that minor, untreated TSH elevation usually normalized, as indicated by repeat measurement. The frequent postpartum continuation of thyroid hormone therapy for those who started the therapy during pregnancy adds to this concern. Although these factors may be contributing to the overmedicalization of pregnancy, a small proportion of women (1.5%) had overt hypothyroidism that would have required treatment.

Data from high-quality RCTs have consistently shown that treatment of minor TSH elevation (i.e., subclinical hypothyroidism) or thyroid peroxidase antibodies in pregnancy has no benefit for the mother, the neonate or the developing child.[4–7] Our study provides a baseline for future comparison that will allow assessment of knowledge translation of this newer evidence. Furthermore, there is evidence of potential harm from treating minor thyroid test abnormalities in pregnancy. In a 9-year follow-up study of an RCT, children of women with minor abnormalities who were overtreated with levothyroxine, compared with children of women who were untreated, more frequently scored above clinical thresholds for symptoms of poor conduct, hyperactivity and autism spectrum disorder.[9] Additionally, higher rates of preterm delivery, pre-eclampsia and gestational diabetes have been observed among women treated with levothyroxine for subclinical hypothyroidism in pregnancy relative to those who were not treated.[18]

Limitations

We used population-level data, so detailed patient information on the specific clinical indications for thyroid testing or initiation of thyroid hormone therapy was not available. To mitigate this limitation, we used a look-back period of 2 years before conception to identify and exclude women with pre-pregnancy thyroid disease, by means of a thorough, comprehensive combination of the following: ICD-9 and ICD-10 diagnostic codes for thyroid disease, prescriptions filled for thyroid hormone therapy or antithyroid medication, and abnormal results on laboratory thyroid tests. Some pregnancies among mothers who lived in Alberta at the time of delivery but whose residence was outside the province in the 2 years before conception may not have been identified as having pre-existing thyroid disease and thus may not have been excluded from this cohort. This limitation likely affected only a minority of pregnancies.

It is not clear from these data why some women with TSH of 10 mIU/L or higher did not receive treatment with thyroid hormone. This may have occurred in part because TSH fell below 4.01 mIU/L in more than 60% of those with repeat TSH measurement. Alternatively, it may have been a result of women not filling prescriptions from their care providers or using thyroid hormone that was not distributed by a pharmacy. Among women with minor elevation of TSH (4.01–9.99 mIU/L), patient characteristics did not differ between those who were and were not treated; however, we cannot rule out unmeasured differences between these groups. Among the women who were treated, it is not possible to know the proportion whose TSH would have normalized without treatment. However, our findings suggest that repeat TSH testing before intervention is warranted, especially among women with initial TSH elevation in the range of 4 to 10 mIU/L.

Conclusion

Current patterns of practice for TSH testing and management may contribute to overdiagnosis and overtreatment of women during pregnancy and post partum. Clinical practice guidelines are needed to give clinicians a stepwise approach, based on the best existing evidence, for deciding whether and when TSH testing should occur. Guidance is also needed as to when it is appropriate to initiate treatment in pregnancy and continue treatment in the postpartum period.

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